A PRIMARY CARCINOMATOID TUMOR (MESOTHELIOMA) OF THE ADRENALS, WITH SARCOMATOUS METASTASES.

By PAUL GERHARDT WOOLLEY, B.S., M.D.,
LATE RESIDENT HOUSE OFFICER IN SURGERY, JOHNS HOPKINS HOSPITAL, BALTIMORE;
GOVERNORS' FELLOW IN PATHOLOGY, M'GILL UNIVERSITY.

Presented by J. G. ADAMI, M.D.,
OF MONTREAL, CANADA.

(From the John H. R. Molson Pathologic Laboratory, McGill University, and the Pathologic Laboratory of the Royal Victoria Hospital, Montreal, Canada.)

The following case, which presents such interesting features, was admitted to the Royal Victoria Hospital in the service of Dr. Stewart, on September 3, 1901. Dr. Stewart has kindly permitted me to report the case, and I wish to express my gratitude to him for this and numerous other courtesies.

The case was that of A. F. I., a machinist by trade, aged forty-two years. His family history was unimportant. He had led a fairly regular life, and was a strong, healthy man. He had no venereal history, but had had typhoid fever when he was twenty-seven years old.

In June, 1901, while at work, he had a peculiar "attack," in which he became unconscious, a state which lasted about twenty minutes, and during this he had some inspiratory distress. Following this attack he was weak and could do only light work. A month later he had another and similar one, which he could feel coming on for about two minutes previous to the seizure. He had had no other attacks. Two weeks before admission to the hospital he began to suffer from headache, which was confined principally to the left frontal region. This lasted until September 1st, and did not recur. On this and the following day he vomited after taking medicine, and about this time began to be conscious of some dimness of vision. Since August 30th he had been rather drowsy and stupid; no particular weakness had been noticed, and no muscular twitchings. At the time of admission to the hospital he was able to walk from the cab to the ward.

The physical examination showed that he was a rather bony adult, somewhat stuporous, but answered questions fairly well. He wandered at times, but was not obstreperous, and there was no evidence of paralysis. When he slept the right eye remained partly open.

During his stay in the hospital his temperature remained subnormal, with the exception of September 3d, when it rose to 100.2° F. He showed no evidence of glandular enlargement; his pulse was regular but of low tension. There was a faint systolic murmur heard at the apex of the heart, not transmitted into the axilla; the second pulmonic sound was accentuated. His appetite was poor; the abdomen was apparently normal. The muscular system was poorly developed. Sensation could not be well determined because of the patient's mental condition. There was ptosis of the left upper eyelid. Reflexes were normal. The urine showed a faint trace of albumin. While in the ward he became restless and would get out of bed to wander about; generally, he was quiet and drowsy.

On September 7th he had incontinence of feces for the first time, and on the 9th optic neuritis was first detected. On September 13th Kernig's sign was present, but lumbar puncture gave a negative result. On September 18th Kernig's sign was more marked; the head was considerably retracted, and he had incontinence of urine and feces. There was a conjunctivitis present on the right side, and the patient was noisy and incoherent. On the 21st Kernig's sign was less marked and the abdomen was retracted; there was no paralysis. He died on this day.

Clinical Diagnosis. Meningitis, cerebral tumor.

Autopsy. The autopsy was performed thirteen hours after death by Dr. Adami. The body was that of a long, lanky, middle-aged man, rigid and slightly livid. The left pupil was irregular, as though from some operation; there was a conjunctivitis of the right eye and a slight erosion of the cornea. The chest was long and narrow; abdomen rather sunken. There was a slight pedunculated papilloma on the inner side of the right knee; feet extended, toes retracted. On the inner side of the lower third of the leg was a small pigmented area measuring 3 x 4 cm., there was also slight pigmentation extending up along the inner side of the right thigh; no increased pigmentation of areas normally darker in color.

Head. The skull-cap was easily removed, the dura was not congested, but was a little opaque. When this was removed the right side of the brain was seen to be full and the convolutions slightly flattened.

Brain. Weight, 1435 gms. No adhesions between the dura and pia; superficial vessels moderately congested; the organ symmetrical. Upon examination of the base a suspicious granular appearance was noticed over the anterior and inferior angles of the temporal lobes. On further examination a small broken-down area discharging grumous material was found at about the middle of the second left inferior temporosphenoidal convolution. The microscope revealed in the discharged material diplococci staining by Gram's method. On section the brain showed in various places irregularly scattered pigmented areas varying in size and depth of color; the smaller ones were just about the same color as the cortex, but were more granular in appearance, the larger ones were dark brown, as from old hemorrhage. These areas were not sharply circumscribed and occurred, for the most part, in the white substance just beneath the cortex. The smaller areas were of firmer consistency than the brain substance, the larger ones were quite friable. There was evidence of slight chronic meningitis about the circle of Willis.

Neck. Pharynx, a few scattered ulcers were found on the right side, with a small amount of pus. Larynx and trachea normal; thyroid well-formed, but a trifle small.

Thorax. Left lung: weight, 565 gms. There were a few firm adhesions at the apex and also along the line of the first rib on the left side; no fluid in pleural cavities. In the apex of the lung was a spiculated calcareous obsolescent tuberculous nodule; otherwise the lung was normal and there was no sign of secondary growth. Right lung: weight, 875 gms. Fairly frequent, small and fibroid obsolescent tubercles were seen in the region of the apex. On the lateral aspect of the upper lobe and about its middle was a firm, roughly spherical mass projecting slightly above the surface. This cut with some resistance and on section had a decidedly cancerous appearance. It measured 3 x 4 x 4 cm. It was mottled with areas of pale brown as from old hemorrhage; a similar but smaller mass was found in the lower lobe near the root of the lung, and one or two miliary nodules of the same nature were found in the substance of the same lobe.

Heart. Weight, 250 gms. The heart was rather small. All the valves, except the mitral, showed fine verrucose vegetations along the lines of apposition of the cusps.

Abdominal Cavity. There were a few translucent lymph cysts in the neighborhood of the head of the pancreas, which could be easily removed from the mesentery.

Stomach, normal; *intestines,* normal.

Liver. Weight, 1352 gms. A small angioma was seen on the surface of the right lobe just above the middle of the anterolateral aspect. The whole organ was slightly congested.

Spleen, normal.

Pancreas, small but apparently normal.

Adrenals. The left adrenal was large and pale and was the seat of several whitish nodules, the largest measuring 11 mm. in diameter. There was another nodule almost the same size, and one that measured 8 mm. in diameter. The right adrenal was larger and contained one large central cancerous mass. Two or three lymph glands in the neighborhood and to the inner side showed a distinct enlargement, and are firm and pale. On the left side in front of the kidney was one firm globular gland which appeared to be partly hemorrhagic, partly cancerous.

Kidneys, normal.

Bladder, normal except for the presence of two small pedunculated polypi.

Anatomical Diagnosis. Chronic basal meningitis; subchronic verrucose valvular endocarditis; ulcerative pharyngitis; ulcer of cornea; primary carcinoma of adrenals, with metastases in the right lung, brain, and peritoneal lymph glands; polypi of bladder; obsolete tuberculosis of both apices.

Microscopic Examination. The tissues had been preserved in Orth's and Zenker's fluids, with the exception of the brain, which had been preserved in formalin. Small pieces of these tissues were treated in the usual way by dehydrating gradually and embedding in celloidin and paraffin. The sections varied in thickness from 3 to 6 μ in paraffin and from 5 to 10 μ in celloidin

These sections were stained with hematoxylin and eosin, thionin, safranin, gentian violet and eosin, Mallory's stain for connective tissue, and by Gram's method in the case of the sections from the lung. They were cleared in xylol or creosote and mounted in Canada balsam. Preparations to show the reticulum were made by Mall's method and stained with nigrosin.

Sections from the kidney, pancreas, and left lung showed no abnormality. There was no sign of new-growth in the heart.

Adrenal. Sections cut through the entire thickness of the gland showed, when viewed with the low power, several nodules of deeply staining tissue, apparently well circumscribed by normal gland substance. One of these nodules was apparently in the fasciculated zone of the gland and was bounded externally by normal glomerulosa, internally by normal medulla, and on the sides by normal fascicularis which above was continuous with the normal zona glomerulosa. When thinner sections of the same nodule were studied with the higher power it was plainly seen that the circumscription was not as well marked as it had seemed upon first examination (Fig. 9). The inner part of the nodule was composed of pure tumor tissue, while its edges were composed of a mixture of this same tissue with normal gland tissue. Upon still closer examination it was readily seen that the transition from true gland to tumor is not abrupt, for in columns of cells—for the most part normal—certain cells were seen that approach the type of cells in the tumor mass (Fig. 1). The cells of the gland were, as usual, rather large cells with perfectly round nuclei; the nuclei relatively palely stained, the protoplasm was either coarsely granular or finely reticulated and stained pink with eosin. As these cells became changed to assume the type of tumor cells, the nuclei became larger and oval, or irregularly shaped, with a deeply staining chromatin network. At the same time the protoplasm took on a rather bluish tinge with the hematoxylin and eosin, and became relatively less in amount.

By such stages a type of cell was produced which was much unlike the normal gland cells, but between these two types all the stages could be followed in a single field of the microscope.

There was one area in the zone of the gland bounding the tumor mass in which the growth had involved the zona glomerulosa. This was apparently not an involvement by simple extension, for there was normal tissue between the large tumor mass and this microscopic one. In this the picture presented was very interesting (Fig. 2), for the whole area was composed of small islands of cells interspersed with other islands of tumor cells which were more nearly of the gland type than of the tumor type. But among the normal cells could be seen occasional transition forms.

Such appearances, together with the fact that the original tumors are bilateral, indicate very plainly, it seems to me, that the growth originated, not in one cell or group of cells which by their growth produced a tumor, but rather in the cells of the glands, which, influenced by some biologic change, lost their physiologic or acquired characteristics, and retained simply their embryonic or formative characteristics.

Then, too, the gradual transition that is seen taking place from normal cells to abnormal tumor cells, completes the evidence of the process.* Cells have not been cut off from their normal relations by fibrous tissue, for the stroma of the tumor is just as much like that of the original gland as it can be, and corresponds well with Flint's pictures of the reticulum. All about the edges of the tumor mass in the adrenal this gradual change can be seen, with no evidence at any place of inclusions.

There was some difference between the cells at the periphery of the nodules and those in the center. In the center they became more elongated, both as to general cell-shape and as to nucleus; their reactions to stains were the same. There were, besides these cells, others with a finely granular protoplasm which showed a very faint violet with thionin; not the pure metachromatosis of the "mastzellen," but approaching it. These occurred between the columns of the tumor cells. The cells of the tumor masses were arranged much like those of the normal fasciculated layer of the gland. At the periphery this arrangement was most complete, in the centre less so. Between the columns were scattered small round cells of formative type with occasional polymorphonuclear leucocytes. Red blood cells were seen in the vessels. There was no evidence of vascular alveolar formation, no evidence of vascular new formation, and no evidence of primary involvement of the connective tissue. Mitotic figures were common, and were regular and irregular in type; multinucleated cells were frequent.

At least the larger part of the supporting tissue was intercolumnar; when a single cell of a small group of cells was surrounded by such tissue it would seem that this was because columns had been cut transversely. A study of the reticulum illustrates this point. By comparing the size of the cells in the sketch of the reticulum (Fig. 5), it will be seen that the meshes of the reticulum are all larger than the largest cells. I am forced, therefore, to conclude that, as in the case of true sarcoma, there is an absence of intercellular network. This conclusion has also been strengthened by carefully staining sections by Mallory's method.

Lung. In the lung, light was shed upon the method of metastasis. Here were very recent growths as well as ones less recent, and the progress of growth could be readily followed. That metastasis had taken place by the venous system was probable both from the history of other cases of malignant tumors of the adrenals (illustrated by those of Leva,[22] Peacock and Bristowe,[24] Thompson,[36] Dickinson,[89] Affleck and Leith,[13] Eberth,[48] Fox,[49] Rosenstein,[60] and Rolleston and Marks[35]), and from the distribution of the metastatic growths. This evidence was completed by the recognition of tumor cells lying free within the bloodvessels. The nodules in the lung are not, apparently, as well circumscribed as in the adrenals, and on closer study this is seen to be due to the fact that the growth follows the bloodvessels.

---

* It is interesting to observe that Jores, describing the one almost identical case which I find on record, makes a like observation. He states: "Die Stellen aus sich nachweisen lässt, das die Geschwulstzellen aus den Parenchymzellen der Nebenniere direkt hervorgehen, sind es, die dem vorstehenden Fall ein besonders Interesse verleihen. . . . . . An manchen Stellen setzten sich die Maschen der Zona fasciculata in das stroma des tumors direkt fort. Die Parenchymzellen der Nebennieren wandelten sich in Geschwulstzellen um. Man sah in einer Alveole noch erhaltene Nebennierenzellen und rundliche Geschwulstzellen nebeneinander liegen. . . . ." (Jores, Deutsch. med. Woch., 1894.)

There are two possible methods whereby this growth, in such intimate relationship to the vessels, has been produced. The fact that tumor cells were free in the blood might indicate that both had come into play. One method is that which results from thrombosis with tumor cells; the other is that resulting from rupture of a tumor mass into the blood stream with consequent transplantation of the cells into the vessel walls without obvious thrombosis. A study of portions of the tumor nodules revealed evidence of the occurrence of both these processes.

In one section of a lung nodule I encountered a vein cut longitudinally, with a mass projecting into its lumen (Fig. 11). A study of the relationships of this projecting mass showed that the condition was that of a nodule of tumor tissue which had developed on the outer side of the vessel wall, had involved all the coats, and had extended along the vessel wall subendothelially. At one place the endothelium had given way and a few cells were liberated and were to be seen free in the lumen.

In another section (Fig. 8) the bifurcation of a vessel was seen to be plugged with a mass of tumor cells; this mass had become covered in the muscular surfaces with endothelium, but from this mass the growth was progressing subendothelially. Of course, the fact that a mass of tumor cells is covered by an apparently normal and intact endothelium is no proof that the growth has taken place primarily beneath that endothelium, for, following transplantation of tumor cells upon endothelial surfaces, the endothelium may increase and completely cover the resulting mass and give rise to the appearance of a subendothelial growth. This is well illustrated in the very interesting case reported by Martin,[100] in which transplantation occurred upon the peritoneum and in which the peritoneal tumors were covered by an intact layer of mesothelium. This case of Martin illustrates also the same subendothelial growth in the vessels that is present in my case.

That this appearance was not the result of a slanting cut could be plainly seen in the section. The subendothelial or perithelial growth can be seen in Figs. 3 and 4.

The cells in the lung metastases varied considerably in appearance with the age of the nodules. In the more recent nodules the cells were polyhedral, with the usual large dark nuclei and small amount of cytoplasm. As the nodules grew the type was changed to a more elongated form which in some places became of the real spindle-celled form.

Here, too, was no evidence of active participation of the connective tissue or of the muscle of the vessel walls of the endothelium. The most that could be said of the endothelium is that it bounded the growth in the blood vessels. In some of the vessels of the lung there were some micro-organisms of the type of diplococci. These were seen in thionin preparations, but were not stained by Gram's method.

Finally, here, as in the adrenal, were considerable numbers of small round cells scattered throughout the tumor masses, and about these masses there was a certain amount of consolidation of the lung with multitudes of polymorphonuclear leucocytes.

Lymph Gland. Section of the lymph gland from the neighborhood of the adrenal showed an almost complete replacement of the normal gland by abnormal cells of the blunt-spindle type; there was no evidence of any special orderly arrangement.

Brain. Sections of very small nodules showed a marked subendothelial growth (Fig. 10). The distribution here for the most part followed the blood supply, and in all but the smallest vessels an intact endothelium could be plainly seen. No new vessel formation was apparent. In the larger tumors there was much hemorrhage, but the type of tumor was the same, except that especially at the periphery of the growths the vessels could not be seen. In some cases the vessels could be seen to be thrombosed by tumor cells. Another method of vascular obliteration is seen in the brain. At one point, and followed in serial sections, there was a papillary growth into the vessel lumen. This growth was composed of tumor cells of long polyhedral or blunt spindle form and supported by a very delicate supporting network; its surface was covered with normal endothelium (Fig. 7).

The cells in the brain tumor differed still more markedly from the cells of the original tumor than did those in the lung metastases. Here the type was in the greater part that of a small round-celled sarcoma; cells with large dark nuclei and with very little protoplasm; in other words, cells of the markedly proliferative type. Some spindle cells did occur, and these about the vessels in the older nodules. Mitosis was very common.

To indicate the relative sizes and the appearance of the cells characteristic of the unaffected gland tissue and of the primary growth, and the metastases in the lung and brain, I have selected with care typical cells from these regions and drawn them with the camera lucida under the same magnification (Fig. 6). The striking differences in size are easily recognizable.

Here, then, was a tumor originating in the cortex of the adrenal, probably in the fascicular layer, which showed in the primary growths adenomatous and epithelial characters, and in the metastases a somewhat alveolar type of round-celled sarcoma verging toward spindle celled, and subendothelial in location.

Such differences between the primary growths and the metastases are remarkable. There have, of course, been cases reported in which two types of primary tumors were present.[15] That this is not such a case I have convinced myself after a very careful study of many sections. The metastasis in the lymph gland just at the side of the adrenal gland has a purely sarcomatous type—very different from the appearance of primary growth. Besides, a study of the embryogeny of the adrenal throws a most significant light on the subject, and, it seems to me, explains the apparent anomaly.

It is true that there have been many differences of opinion existing among the embryologists on the subject of the origin of the adrenal bodies, but now the subject seems to have been settled. Flint,[13] in his monograph, epitomizes the subject up to 1900. Since then a very valuable paper has been published by Aichel,[70] who makes a very careful study of the adrenal from the standpoint of comparative embryology, with the result that he has described both in words and by drawings the complete series of the steps in the development of the adrenals from the lower vertebrates to man.

The old idea was that the adrenal was composed of a mesoblastic part which corresponds to the adult cortex of the gland, and an epiblastic part, corresponding to the medulla. This view has been the prevalent one up to quite recently, and it was elaborated and substantiated by Balfour, Mitsukuri, and Inaba. Janosik and Gottschau, however, held that the cortex was mesoblastic and that the medulla was in turn derived from the cortex, and these authors' views were accepted by Minot.

Flint[13] makes some interesting observations which are but modifications of those of Minot, Janosik and Gottschau. He says: "The cortex of the medulla* (gland) is first formed and then the medulla appears as small groups of cells beneath the capsule, which begin to grow into the cortex. They begin their migration in (pig) embryos from 6 to 8 cm. long, and reach the central vein when the embryo is between 12 and 15 cm. in length. When this point is reached there is a gradual increase in complexity of both cortex and medulla until the adult structure is reached."

As he says, also, that islands of medullary cells may remain in the cortex, it is plain that there is a chance for cortical tumors to be medullary in origin. (That this is not the case in the present tumor is beyond doubt, for all the changes can be traced with little or no difficulty to true cortical substance.)

The only difference between this view of the origin of the medulla of the organ and that of Minot, Janosik and Gottschau is that these observers hold that the medulla is derived from internal layers of the cortex.

Aichel discusses the question of the genesis of the adrenal in a very thorough manner. This author studied the matter from the

---

* The use of "medulla" here is evidently not intentional, and due probably to an oversight. By the context it is very plain that Flint means "the cortex of the gland."

standpoint of comparative embryology with most gratifying results—gratifying in this, that he was able to obtain parallel and concordant observations from the lowest to the highest forms of vertebrates. He comes to the conclusion that the interrenal bodies of the lower vertebrates correspond to the adrenals of the higher vertebrates, and that both arise from the "urniertrichter,"* and the "urniertrichter" is of mesothelial origin, to employ Minot's term. The "Marchand's adrenals," or the supernumerary adrenals found in the broad ligament of the female and near the prostate and spermatic cord in the male are, he found, derived from the segmental tubules of the Wolffian body, and correspond, therefore, to the suprarenals in the lower vertebrates.

The other adrenal tissue, such as occurs in the right lobe of the liver and in the kidney and in the adrenal itself, may be true adrenal tissue that has been separated from the rest of the anlage. That cortex and medulla arise from the same Wolffian body cells, he states confidently, and his account reads very much like that of Flint.

It appears, then, that, dismissing the older view of Balfour, Mitsukuri, and Inaba, the adrenal bodies are primarily of mesothelial origin. By using "mesothelial" rather than "mesodermal," I mean that the gland in its adult form is a derivative of that portion of the mesoblast which later comes to line the body cavities—*i. e.*, pleura, pericardium, and peritoneum, and the cavities formed from peritoneum. A review of the main facts of the history of the genesis of the embryonic layers may assist in a better understanding of the facts before us.

From the one-cell stage the ovum proceeds, after fertilization, to the multicellular stage. At an early period these cells form a single layer, which later multiplies to form two layers, the "ectoderm" and "entoderm." Later still, between entoderm and ectoderm there appear certain cells which are the primitive elements of "mesoderm." These latter are gradually differentiated into two groups, part of them, the group nearest the medullary groove—the mesenchymal anlage—remain as a mass, from which later the connective tissues are derived, together with possibly the blood and bloodvessels and the spleen; those farthest from the medullary groove become separated into layers, and the superficial cells of the splanchnopleuric and somatopleuric mesoblast, the lining cells of the primitive body-cavity, give rise in later stages to the serous membranes, the urogenital tract (except the bladder), and striated muscle. So it is seen that with a common origin the mesothelial element becomes more highly differentiated than the mesenchymal, and acquires in a certain degree the so-called "epithelial" characters; by which is meant that the cells are more or less independent of a direct blood supply, that they are covering cells and that they have no true supporting membrane, but are united by a simple undifferentiated cement substance.

---

* Aichel's illustrations show very well what he means by "Urniertrichter," or "Wolffian body funnels."

It is also plainly evident that if the laws of specificity of the germ layers hold good in the reversion of the mesenchymal tissue, it will be easier for it to revert to the primary mesodermal type than it will be for a mesothelial one to do the same, but that mesothelium in spite of its acquired epithelial characters may ultimately in its reversion become in type that of mesoderm.

If we start with the two propositions, first, that the characters of neoplastic cells are not of the nature of new acquirements, but on the contrary are reversionary; and second, that characters most recently acquired are those which are first lost (as Virchow has intimated), and those first acquired are the last to be replaced, then we may say, that, although all tissues of the body are derived from a single cell whose progeny have become differentiated more and more, yet all tissues will not revert with equal ease to the stage of completely undifferentiated cellular structure, and that structures of epiblastic and hypoblastic origin will retain their lining membrane characteristics with greater tenacity than those of mesoblastic origin, whose lining membrane characters have been assumed at a later date, even after previous differentiation in the original middle layers of the embryo. In other words, mesothelial tissues in assuming regressive and proliferative peculiarities will more readily lose their epithelial qualities than will epiblastic or hypoblastic tissues and sooner and more easily reach the primitive morula type. And for the same reason we may believe that cells of mesenchymal origin will reach the primitive type more easily than will mesothelium. And so it is comprehensible that tumors of mesothelial origin, while they may retain epithelioid properties, may also manifest all the appearances of true sarcomata. As Jores states, "Ferner kann man nicht gerung betonen, das Sarkome des Nebennieren häufig einen den Carcinomen überaus ähnlich Bau zeigen." (Jores, *loc. cit.*)

It is upon these grounds that the variations in the tumors of testis, ovary, kidney, and suprarenal, all organs of mesothelial origin, can be most logically explained. But these appearances make it plain that our nomenclature for these tumors, as well as our conception of their relationships, must be materially modified.

It is apparent that, embryogenetically speaking, cancer of the urogenital tract is impossible except in the bladder—if that is a term employed only to denote atypical tumors of epiblastic or hypoblastic origin—that all malignant tumors of this tract must be sarcomata; if, that is, we accept this definition that atypical tumors of mesoblastic origin are sarcomata. This use of terms leads us into such difficulties that it would seem wise in the case of the mesodermal tumors, at least, to break away from the traditional terms "sarcomata" and "carcinomata," which are only confusing, no matter upon what basis the nomenclature rests. A good example of the confusion is the case of the tumor described in this paper. If we call it carcinoma we must do so on purely morphologic grounds; and what shall we say of the metastases? They are sarcomata on the same grounds. If we call it sarcoma, it must be on purely embryologic grounds, and it certainly does not look like the sarcoma, even though it be such, logically. But confusion is also caused here by the absence of correlation between the old nomenclature and the morphologic appearances of tissues. Grawitz, Horn, and Sudeck call tumors of adrenal rests carcinoma or sarcoma, a nomenclature which evidently depends upon appearances. Speaking narrowly, malignant tumors of the adrenal can be nothing but sarcomata. Rolleston and Marks[35] state this very well when they say: "Our own impression is that malignant tumors of the suprarenal bodies are peculiar and form a special class. They may approach structurally either the carcinomata or the sarcomata, and sometimes one and the same tumor may in different parts resemble both."

Since the suprarenal bodies may be regarded as mesoblastic from a developmental point of view, and as epithelial from the morphologic, it is perhaps natural that it is not always easy to assign the tumors that arise in them to either the mesoblastic (sarcomatous) or epithelial (carcinomatous) group of tumors. It is conceivable then that many, though not necessarily all, of the sarcomata arising in the suprarenal bodies are, like carcinoma, derived from the proliferation of secreting cells of that organ.

It seems wise, therefore, to call this tumor a "mesothelioma," following the example of Buxton[98] and the timely suggestion of Minot, that we call serous membranes and their derivatives mesothelium, and also following the suggestions of Adami in his work on classification.* The application of these observations to the tumors of the adrenal gland sheds a very significant light on pathologic processes, and the relationship of embryology and pathology becomes closer, as Minot[1] desires it shall.

When cells in their development gradually lose their embryonic characters to take on more complex ones, their spheres of activity are gradually narrowed, until in the final stage of development there is but one permanent character which remains, and while the cell is functioning normally it cannot do less than carry on its physiologic work. The neuron is the type of this highest stage of development; if it stops it dies; it cannot reproduce. Other cells less highly differentiated have left to them some part of their embryonic characters, and, according to their position, more or less of it. To accomplish their physiologic labor they must be able to reproduce, but while reproduction goes on the more complex function declines to be renewed when reproduction has ceased. When growth and reproduction are at their maximum physiologic function is lost. In other words, the cell has reverted toward the embryonic type, has degenerated, to speak broadly; or, as Adami[7 8] urges, has assumed vegetation and proliferation in place of functional characters.

This reversion toward the embryonic type is what happens in tumor formation, and which culminates in the malignant tumors. In the benign tumors the specific function of the cells is overbalanced by the embryologic one; in the malignant tumors it is lost.

Now, it is true, probably, that "progress and differentiation act as a progressive restriction of further development. Each successive stage of differentiation puts a narrower limitation upon the possibilities to further advance. Applied to pathology the law means that the range of possible pathologic changes is determined not merely by the nature or kind, but also by the stage or degree of the previous differentiation of the tissue (Minot)." And further, the law means that "when cells revert to the embryonic condition, as so often happens in pathologic processes, they never attain such a degree of prematurity that subsequent differentiation is possible with other functions (Le Conte)." (There are some apparent exceptions.)

---

* An address soon to be published in the Journal of Pathology.

So we have in the development of cells a limitation in the differentiation, progressive and regressive. Ectothelium never becomes more or less than ectothelium, and the same is true of the other tissues. The only difference lies in the fact that the most variously differentiated tissue may show more various features in reversion, as is true in tissues of mesodermal origin.

We can now see that the changes in the tumor described above are in harmony with the laws of histogenesis. Such a series of changes as has been depicted indorses and emphasizes the results of embryologic study of the adrenal bodies. Cells that undergo such changes can have but one origin according to this law, they must be mesothelial. So, as Minot says, "It is more than probable that all pathologic tissue is as strictly governed by the law of specific value of the germ layers as are normal tissues." This law holds in reversion as in development.

This state of affairs is voiced by Lubarsch[64] in the following words: "So bald eine Zelle biologisch als Epithel- oder Bindegewebszelle in weitesten Sinne differenzirt, kann aus ihr nur noch eine gleichartige Zelle werden."

It will suffice, I think, at this time to remark that, in looking over the literature for primary carcinomatoid tumors of the adrenals, and subjecting the reports to the criteria laid down by Rolleston and Marks,[35] I have been able to find twenty-one cases besides my own. At a later date I shall collect my notes and publish them. For the present I will simply state that the cases I have selected, which were well-described microscopically and which showed metastases, are those of Fenwick,[35] Brooks[35] (two cases), Carriere and Delearde,[42] Pawlick,[17] Rolleston and Marks[35] (three cases), Ogle,[23] Ritchie and Bruce,[25] Weinburg and Turguet,[40] Brüchnow[18] (three cases), Orth[94] (two cases), Marchand,[95] Collinet,[19] Stoukoventoff,[71] Possett,[96] and Hansmann.[21]

CONCLUSIONS—SUMMARY.

1. Carcinomatoid tumors of the adrenals are rather uncommon, only twenty-one cases being on record.

2. The application of the terms "carcinoma" and "sarcoma" to tumors of mesothelial origin is misleading, and may be discontinued with benefit. The term "mesothelioma" is a better term.

3. Regressive changes in neoplastic tissues correspond to relative losses of physiologic function and relative gains in formative characters.

4. Tumors of mesothelial origin may vary in type in their primary

growths and in their metastases, and these variations are evidences, in reversion, of the various stages in the genesis of the tissue in which the tumors originate.

5. The tumor described above is a malignant mesothelioma of epithelial type (mesothelioma malignum carcinomatoide).

I desire now to thank Dr. Adami for his gracious kindness and ever-present encouragement to me in my work.

Bibliography.

1. Minot. The Embryologic Basis of Pathology. Science, 1901, N. S., xiii. p. 481; and Boston Medical and Surgical Journal, 1901, cxliv. pp. 295–305.

2. Morris. The Surgery of the Kidney (Lecture IV.). British Medical Journal, 1893.

3. Murchison. Cancerous Growth in the Right Suprarenal Capsule. Transactions Pathological Society, London, 1857–8, ix. p. 400.

4. Murchison. Cancer of One Suprarenal Capsule Without any Symptoms of Addison's Disease. Ibid., 1867–8, xix. p. 416.

5. Ashhurst. The International Encyclopedia of Surgery, New York, 1884, v. p. 1087.

6. Williams. Malignant Tumors of Early Life. Lancet, 1897, i. p. 1261.

7. Adami. The Habit of Growth. Montreal Medical Journal, 1895–6, xxiv. p. 581.

8. Adami. On Growth and Overgrowth, and on the Relationship Between Cell Differentiation and Proliferative Capacity. Its Bearing Upon Regeneration of Tissues and the Development of Tumors. Festschrift in honor of A. Jacobi, 1900.

9. Adami. The Causation of Cancerous and Other New-growths. Brit. Med. Journal, 1901.

10. Ambrosius. Beitrag. zur Lehre von der Nierengeschwülste. Diss., Marburg, 1891.

11. Auld. Preliminary Report on the Suprarenal Gland and the Causation of Addison's Disease. British Medical Journal, 1894.

12. Beneke. Zur Lehre von der Versprengung von Nebennierenkeimen in der Niere nebst Bemerkungen zur allgemeine Onkologie. Ziegler's Beiträge, 1891, ix. p. 440.

13. Flint. The Bloodvessels, Angiogenesis, Organogenesis, Reticulum, and Histology of the Adrenal. Contributions to the Science of Medicine, Baltimore, 1900.

14. Israel. Maligne Struma der Niere. Berlin klin. Woch., 1892, No. 26.

15. Walter. Ueber das multiple Auftreten primärer bosärtiger, Neoplasmen. Archiv für klin. Chir., 1896, liii.

16. Ruyter. Congenitale Geschwülst der Leber und beider Nebennieren. Archiv. f. klin. Chir., 1890, xl. p. 98.

17. Pawlick. Casuistischer Beitrag zur Diagnose und Therapie der Geschwülste der Nierengegend. Archiv f. klin. Chir., 1896, liii. p. 530.

18. Brüchanow. Zur Kenntniss der primärer Nebennieren Geschwülste. Zeitsch. f. Heilk., 1899, xx. p. 41.

19. Collinet. Épithélioma de la Capsule Surrenale droite. Bull. Anat. Soc., Paris, 1892, p. 325; Cent. f. Allg. Path., 1892, iii.

20. Averbeck. Die Addison'sche Krankheit. Erlangen, 1869.

21. Hausmann. Primäres Krebs beider Nebennieren. Berlin. klin. Woch., 1876, xlv. p. 648.

22. Leva. Zur Lehre des Morbus Addisonii. Virchow's Archiv, 1895, cxxv. p. 35.

23. Ogle. Unusually Large Mass of Cancerous Deposit in One of the Suprarenal Capsules. Transactions Pathological Society, London, 1864, xvi. p. 250.

24. Peacock and Bristowe. Cancer of the Suprarenal Capsules and of Other Organs. Ibid., 1856, viii. p. 333.

25. Ritchie and Bruce. Notes on a Case of Carcinoma of the Suprarenal Capsules and Lungs. Transactions Medico-Chirurgical Society, Edinburgh, 1889, N. S. ix. p. 67; Edinburgh Medical Journal, 1890, xxxvi. p. 12.

26. Schuchardt. Mittheilung eines Falles von Carcinom beides Nebennieren und der Schilddrüse mit krebsiger Thrombose des Ductus Thoracicus. Breslauer Arztl. Zeitschr., 1883, No. 17.

27. Gibbs. Cancer of the Suprarenal Capsules. Transactions Pathologic Society, London. viii. pp. 255, 340.

28. Heitler. Krebs der Rechten Nebennieren. Wien. med. Presse, 1875, xvi. pp. 809–833.

29. Kerulg. Ein Fall von Nebennieren- und Leber-krebs. St. Petersb. med. Wochenschr., 1888, N. F. V., p. 63.

30. Lubet-Barbon. Cancer de la Capsule Surrénale. Bull. Anat. Soc., Paris, 1885, lx. p. 136; Prog. Med., 1885, II ser. ii. p. 556.

31. McGillivray. On a Case of Cancer of the Suprarenal Capsules. Australian Medical Journal, 1868, xiii. p. 294.

32. Nuno Porto. Encephaloïde Primitivo da Capsula Suprarenal. Med. Contemp., Lisbon, 1884, ii. p. 188.

33. Sapalier. Carcinome Primitif de la Capsule Surrénale. Bull. Anat. Soc., Paris, 1881, lvi. p. 267; Prog. Med., 1881, ix. p. 793.

34. Stybr. Dva prvothe Karcinomy nadledonik bez nemoci Addisonovy (Quoted by Brüchanow). Sboru lév. v. Praza, 1890, iv. p. 84.

35. Rolleston and Marks. Primary Malignant Disease of the Suprarenal Bodies. American Journal Medical Sciences, 1898, cxvi. p. 383.

36. Thompson. On a Case of Carcinoma of the Pleura, Liver, and the Left Suprarenal Capsule, with Ascites. Medical Times and Gazette, 1874, i. pp. 31–33.

37. Wilkes and Moxon. Lectures on Pathologic Anatomy. London, 1875. (Quoted by Ashhurst.)

38. Dickinson. Cystic Kidney with Carcinomatous Suprarenal Capsules. Transactions Pathologic Society, London, 1894, xlv. p. 128.

39. Berdez. Tumeurs des Capsules Surrénales. Archiv de Med. Exp., 1892.

40. Weinburg and Turquet. Cancer des deux Capsules Surrénales avez noyau métastatique du cervelet. Bull. Anat. Soc., Paris, 1897, p. 751.

41. Wigglesworth. Primary Carcinoma of the Right Suprarenal Capsule. Liverpool Medico-Chirurgical Journal, 1892, xii. p. 254.

42. Carrière and Deléarde. Épithélioma atypique symmétrique des capsules surrénales. Arch. de Med. Exp., 1900, p. 28.

43. Affleck and Leith. Sarcoma of the Suprarenal Capsules. Edinburgh Hospital Report, 1896, iv. p. 278.

44. Berdach. Ein Fall von primären sarkom der Nebennieren. Wien. med. Wochenschr., 1889, xxxix. p. 357.

45. Blackburn. Sarcoma of the Suprarenal Capsules. Journal American Medical Association, 1888, x. p. 389.

46. Cade. Sarcom af Binyrene. Förh. Norske. Med. Selsk., Kristiania, 1886.

47. Cohn. Primäres Nebennieren sarkom bei einen neunmonatlichen Kinde. Berlin. klin. Wochenschr., 1894, p. 266.

48. Eberth. Sarkom der Nebennieren, etc. Arch. f. Path. Anat., Berlin, 1881, liv. p. 21.

49. Fox. A Case of Primary Sarcoma of the Left Suprarenal Capsule. Transactions Pathologic Society, London, 1884, xxxvi. p. 460.

50. Fränkel. Ein Fall von doppelseitigen, völliglatent verlaufen nebennieren tumor, etc. Arch. f. Path. Anat., ciii. p. 244.

51. Greenhow. Cancer of One Suprarenal Capsule. Transactions Pathologic Society, London, 1866, xviii. p. 260.

52. Jones. Ueber Nebennieren sarkom, Deutsch. med. Wochenschr., 1894, p. 208.

53. Kussmaul. Melanotic Sarkom der Nebennieren. Würtzb. med. Zeitschr., 1863.

54. Lazarus. Primary Sarcoma of the Left Suprarenal Capsule in a Child. Medical Press and Circular, London, 1894, p. 467.

55. Merkel. Erkrankungen der Nebennieren. Ziemssen's Handb. der Spec. Path. u. Ther. Leipzig, 1874.

56. Perry. Sarcoma of the Suprarenal Capsules Simulating Addison's Disease. British Medical Journal, 1888, p. 1382; Ibid., 1889, p. 766.

57. Pilliet. Sarcome Primitif de la Capsule Surrénale. Bull. Soc. Anat., Paris, 1888, lxiii. pp. 672, 716.

58. Pilliet. Adenomes des Capsules Surrénales. Ibid., 1888, 1889, 1892.

59. Ramsay. A Study of Sixty-seven Cases of Primary Malignant Tumors of the Suprarenal Gland. Johns Hopkins Hospital Bulletin, 1899, p. 20.

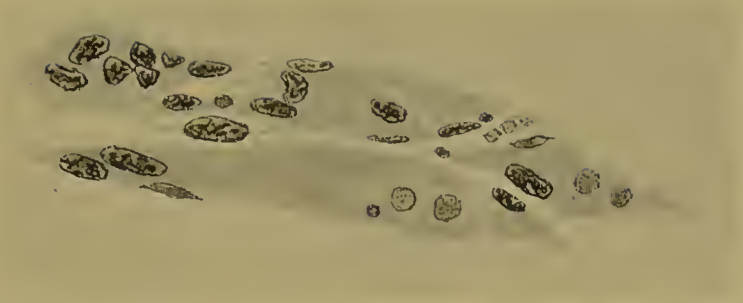
60. Rosenstein. Sarkom der Nebenniere mit Mitastasen in Nieren, Pancreas und rechten Hertzen. Arch. f. Path. Anat., 1881, lxxxiv. p. 322.

61. Smith. Cystic Sarcoma of Right Suprarenal. Dublin Journal of Medical Sciences, 1876.

62. West. Primary Sarcoma of the Suprarenal Capsules, etc. Transactions Pathologic Society, London, 1878, xxx. p. 419.

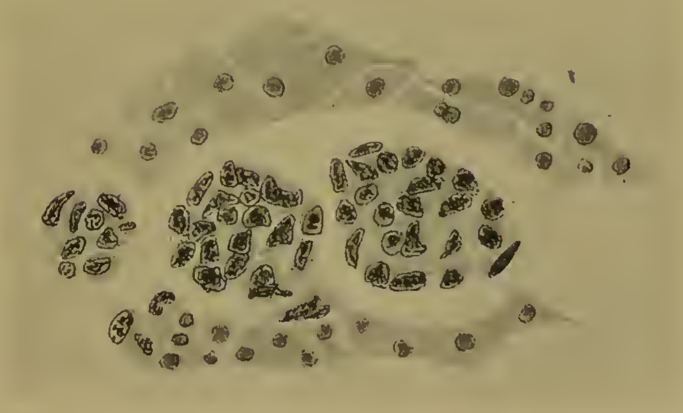
63. Griffiths. Cases of Addison's Disease. British Medical Journal, 1889, p. 242.
64. Lubarsch. Beiträge zur Histologie der von Nebennieren ausgehende Nierengeschwülste. Arch. f. Path. Anat., cxxxv. p. 143.
65. Coates. Glasgow Medical Journal, 1872.
66. Martineau. De la Maladie d'Addison. Paris, 1863.
67. Thornton. Surgery of the Kidneys. London, 1890.
68. Troisier. Ganglion sus-claviculare gauche dans un cas de la Capsule surrénale, etc. Bull. et Mém. Soc. Méd. Hôp., Paris, 1890, 3s. viii. p. 266.
69. Martin. Tumor du vein droit. Lyon Médicale, 1896, lxxxii.
70. Aichel. Vergleichende Entwicklungsgeschichte u. s. w. der Nebennieren. Arch. f. Mikroskop. Anat., 1900, lxv. p. 1.
71. Stoukoventoff. Cancer des Capsules Surrénales. Gaz. Méd. de Paris, 1895, xlix. p. 581.
72. Carrington. Blood Cysts of the Adrenal. Transactions Pathologic Society, London, 1885, xxxvi. p. 454.
73. Fleiner. Zur Pathologie der Addison'sche Krankheit. Berlin. klin. Wochenschr., 1889, li. p. 1101.
74. Haldane. Cancer of Suprarenal Capsules without Bronzing of the Skin. Edinburgh Medical Journal, 1861, vii. p. 586.
75. Hadden. Cancer of Both Suprarenals. Transactions Pathologic Society, London, 1885–86, xxxvii. p. 515.
76. Lancereaux. Les Rapports des lésions des Capsules Surrénales et de la Maladie d'Addison. Arch. Gen. de Med., 1890, p. 5.
77. Sibley. Epithelial Cancer of One of the Suprarenal Capsules. Transactions Pathologic Society, London, 1858, x. p. 272.
78. Wilks and Hutchinson. Report on Dr. Gibb's Specimen of Cancer of the Suprarenal Capsules. Ibid., 1856, viii. p. 340.
79. Zimmerman. Malignant Disease of the Lower End of the Colon, Upper Part of Rectum and Left Suprarenal Capsule. Canadian Journal of Medical Sciences, 1882, vii. p. 390.
80. May. Zur Pathologischen Anatomie der Nebennieren. Virchow's Archiv, 1887, cviii.
81. Osler. Practice of Medicine. Philadelphia, 1898, 1901.
82. Neusser. Die Erkrankungen der Nebennieren. Nothnagel's Handb., Wien, 1897.
83. Ribbert. Lehrbuch. der Allgemeine Pathologie, Leipzig, 1901.
84. Rolleston. Lectures on the Suprarenal Bodies. British Medical Journal, 1895.
85. Addison. On the Constitutional and Local Effects of Diseases of the Suprarenal Capsules. London, 1855.
86. Alexander. Untersuchungen der Nebennieren. Beitr. v. Ziegler, 1891, xi.
87. Besnier. Dégénérescence Cancereux Complète des Deux Capsules Surrénales. Bull. Anat. Soc., Paris, 1850, xxxii. p. 85.
88. De Paoli. Contributio allo Studio dei Tumori Primitivi delli Capsule Surrénale. Anno d. insegn. Chir. d. F. Durante n. Univ. di Roma, Rome, 1898, i. p. 219.
89. Dickinson. On Renal and Urinary Affections, London, 1885, iii.
90. Kelynack. Adrenal Growths. Medical Chronicle, 1897, n. s. viii. p. 409.
91. Klebs. Handb. der Spec. Path. Anat., Berlin, 1876.
92. Cayley. Cancer of the Right Suprarenal Capsule. Transactions Pathologic Society, London, 1864–5, xvi. p. 250.
93. Roberts. Sarcoma Arising Near the Kidney. International Clinics, Series III. i. p. 203.
94. Orth. Arbeiten aus dem Pathologischen Institut in Göttingen. Göttingen, 1893, p. 75.
95. Marchand. Beiträge zur Kenntniss der Normalen u. Path. Anat. der Glandula Carotica u. der Nebennieren. Virchow's Festschrift, 1891, i.
96. Posselt. Berichte über fünf zur Obduction gelangte Fälle von Morbus Addisonii. Wien. klin. Wochenschr., 1894, p. 630.
97. Lubarsch and Ostertag. Ergebnisse der Spec. Path. Morphologie u. Physiol. Wiesbaden, 1896.
98. Buxton. Classification of Tumors. Journal Cutaneous and Genito-Urinary Diseases, 1890, xviii. p. 74.
99. Le Conte. The Rôle of the Endothelium in Inflammation. Journal American Medical Association, 1901, xxxvii. p. 1521.
100. Martin. On Some Undescribed Lesions in Lymphosarcomatosis (Hodgkin's Disease). Journal Medical Research, 1901, vi. p. 249.
101. Ribbert. Lehrbuch der Pathologischen Histologie, Bonn, 1896.

FIG. 1.



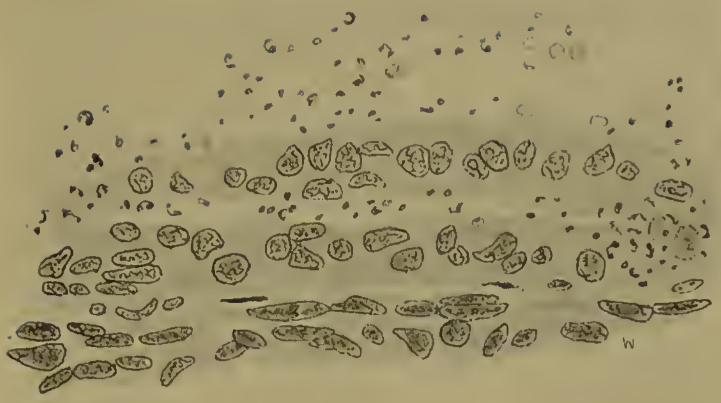
Adrenal. Transition from true gland to tumor. Hematoxylin and eosin. Leitz. Obj. 6, Oc. 5.

FIG. 2.



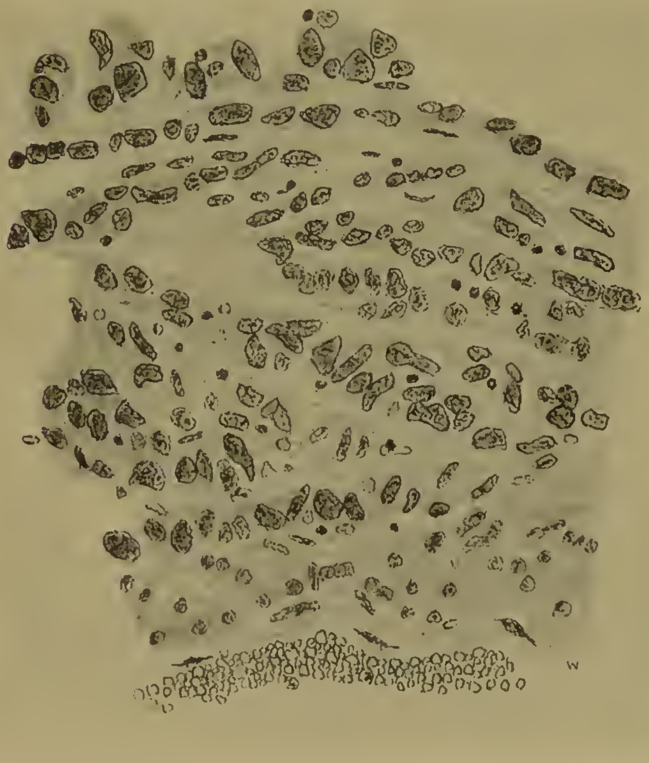
Adrenal. Transition in the zona glomerulosa. Hematoxylin and eosin. Leitz Obj. 6, Oc. 4.

FIG. 3.



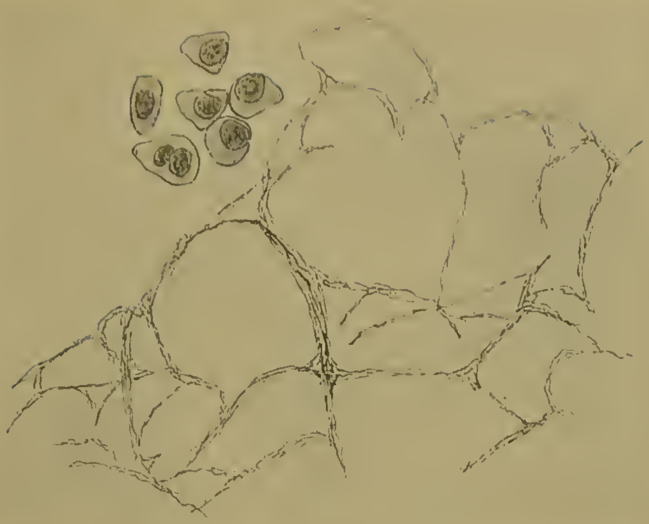
Lung. Wall of a bloodvessel. In lumen a couple of strands of tumor cells. (Camera lucida.) Hematoxylin and eosin. Leitz Obj. 6, Oc. 1.

FIG. 4.



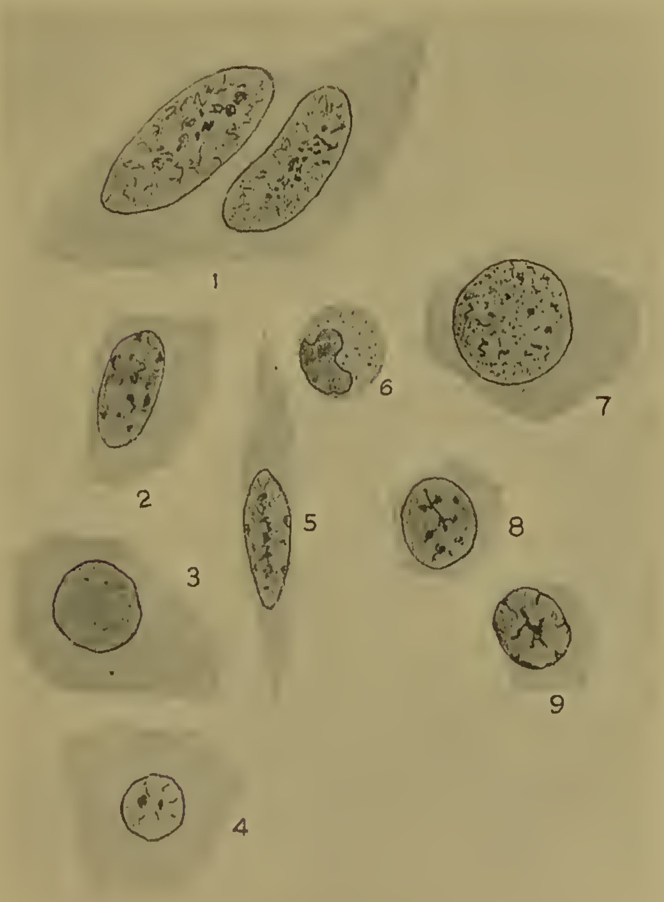
Lung. Wall of bloodvessel showing subendothelial growth with "layer" structure. (Camera lucida.) Hematoxylin and eosin. Leitz Obj. 5, Oc. 1.

FIG. 5.



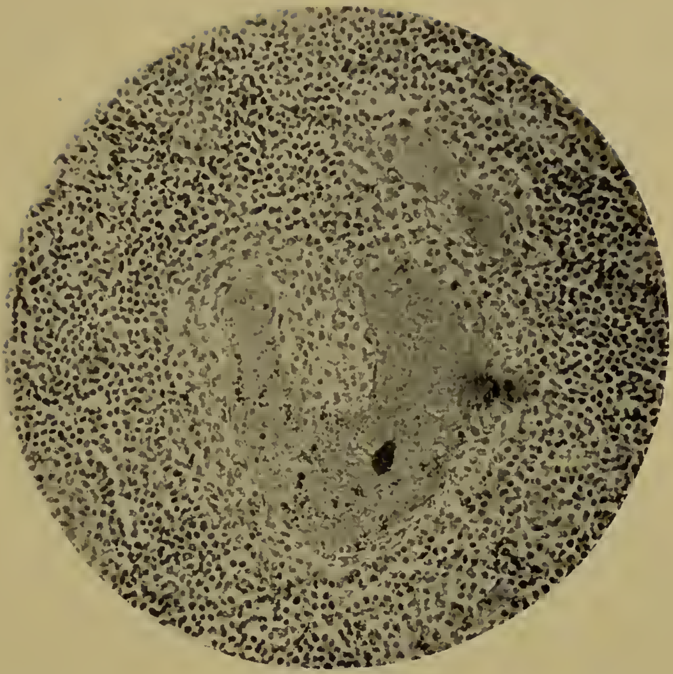
Reticulum of adrenal tumor, with cells from corresponding section. Hematoxylin and eosin. Leitz Obj. 6, Oc. 1. (Camera.)

FIG. 6.



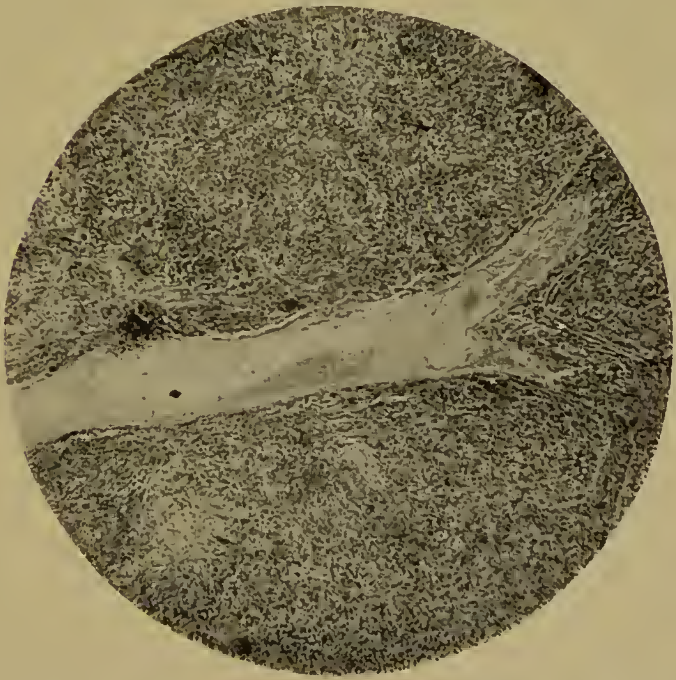
Cells from tumor and metastases. 2, 3. Adrenal. 1, 5, 7. Lung. 8, 9. Brain. 4. Normal adrenal. 6. Leukocyte. Hematoxylin and eosin. Leitz 1/12, Oc. 4. (Camera.)

Fig. 7.



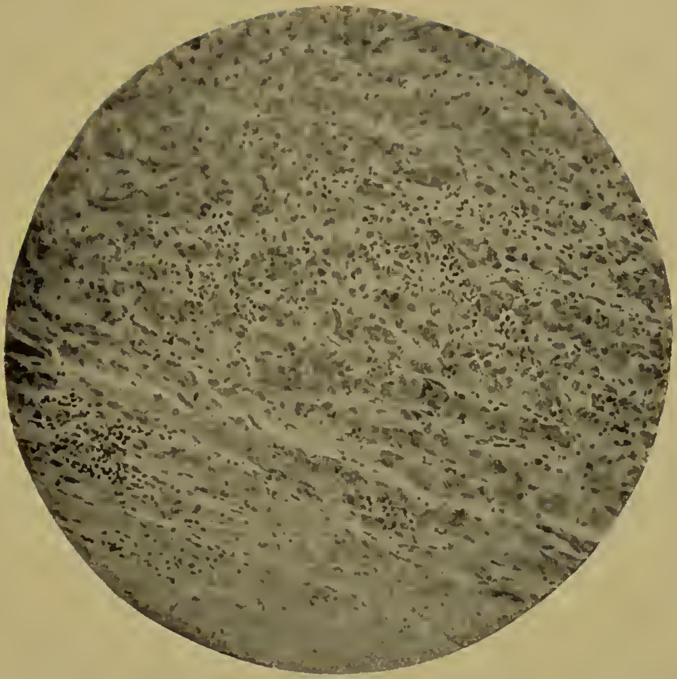
Brain. Intravascular polypus composed of tumor cells covered with intact endothelium and springing from the perithelial subendothelial growth. Photomicrograph.

Fig. 8.



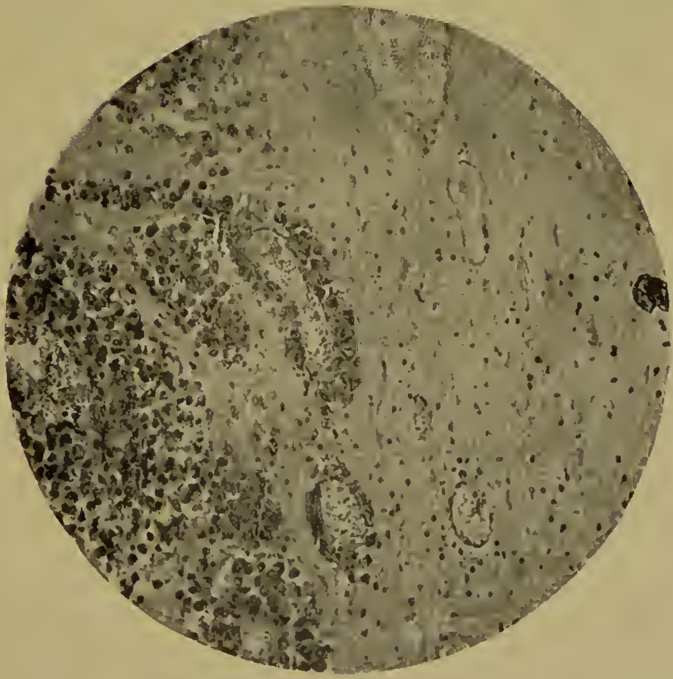
Lung. Thrombosis of a vein with tumor cells showing subendothelial progression. Photomicrograph.

Fig. 9.



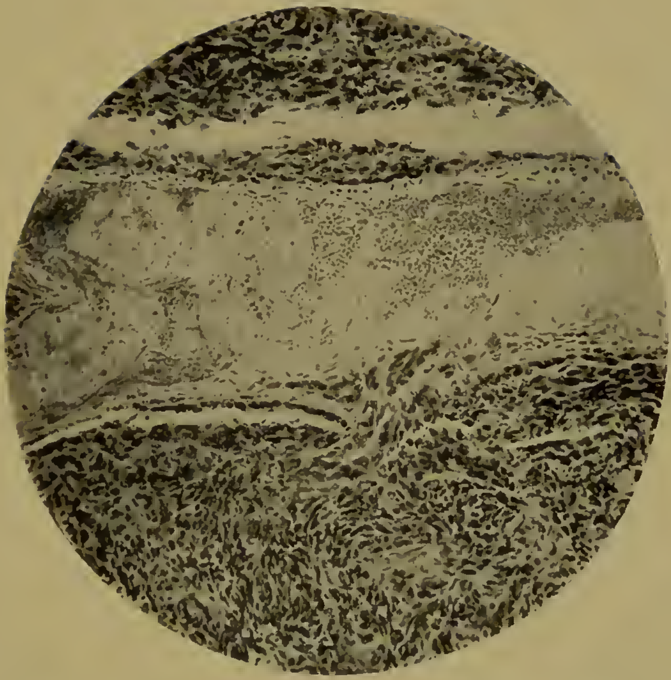
Adrenal. Edge of tumor bounded by adrenal gland substance. Photomicrograph.

Fig. 10.



Brain. Early endothelial growth about bloodvessels. Photomicrograph.

Fig. 11.



Lung. Rupture of tumor into bloodvessel. Photomicrograph.